



## **DISCLOSURE OF CONFLICTS OF INTEREST**

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**American College of Phlebology  
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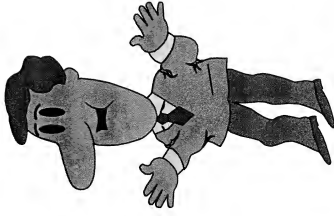
**SESSION 7: FDA Evaluation Process of Foam Sclerosants**

**I do not have any relevant financial relationships  
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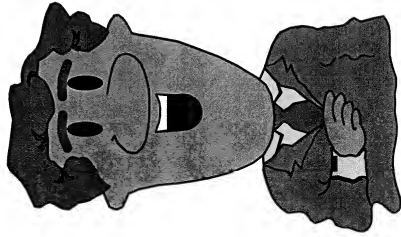
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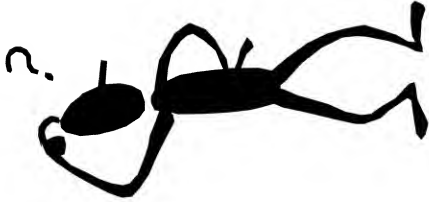
# FDA Evaluation of Foam Sclerosants - What do we look for?



**Safety!**  
**Efficacy!**



# FDA Evaluation of Foam Sclerosants



What is taking so long for the approval  
of aethoxysklerol (polidocanol)?



**Reports of serious adverse events related to treatment  
of varicose veins with sclerosing agents**  
(ODS Reporting Period: Mar-2002 to Oct-2004)

**Deaths**

1 with aethoxysklerol (WHO)  
4 with STS (US)

**Serious Adverse Events**

42 = Allergic reactions including 4 = anaphylactic shock (with  
aethoxysklerol)  
2 = Pulmonary Embolism (with STS)

(These reporting systems typically under-report by a factor of 10 or  
more.)



**Reports of serious adverse events related to treatment  
of varicose veins with sclerosing agents**  
(ODS Reporting Period: Mar-2002 to Oct-2004)

Sclerosing agents can cause Serious Adverse Events (SAEs), including deaths.

These SAEs are probably rare - we don't know how rare.

For approval, FDA needs better characterization of how frequently these SAEs occur.



## Detect Effect of Foam Sclerosants on endothelium of:

- Large veins
  - Endocardium
  - Pulmonary artery
  - {in patients with patent foramen ovale (PFO)}
- cerebral circulation, hepatic and renal arteries



## **Detect Effect of Foam Sclerosants on endothelium of Large veins**

Duplex ultrasound of leg veins (microfoam is visible on  
Doppler):

Track intravascular trajectory of the microfoam



## **Detect Effect of Foam Sclerosants on the Heart**

**One recent (24-Mar-05) report:**

**A patient developed generalized seizures, incontinence of urine and apnea, had to be resuscitated, and was hospitalized for 1 week.**

**Reason = Cardiovascular problem**



## **Detect Effect of Foam Sclerosants on the Heart**

### **Transthoracic echocardiogram**

#### **At baseline:**

R/o cardiomyopathy

Bubble study (+Valsalva maneuver) to detect Patent Foramen Ovale (population incidence  $\cong$  27.3%), ASD, ASA

#### **Post-injection**

To ensure foam is not flipping around in heart chamber

### **\*12-Lead ECG**

At baseline, post-treatment and 24 hours

### **\*CPK, CK-MB, Troponin T (2<sup>nd</sup> generation assay)**

At baseline, and q8H x 3

***\*If abnormal, monitor patient in hospital till resolved.***



## **Detect Effect of Foam Sclerosants on Brain**

**Detection of micro-infarcts in patients with microbubbles in MCA**

### **Screening baseline neurological test and visual field test**

- (1) One patient: tremors of right hand and dysgraphia.**
- (2) Two patients: visual disturbances (one had hypoesthesia)**
- (3) One patient: visual migranous aura and numbness of the other leg just after injection. Next sclerotherapy session cause the same symptoms.**

**Symptoms and signs appeared a few minutes after injection, lasted a few hours, and recovered without sequele.**



## **Detect Effect of Foam Sclerosants on Brain Detection of microbubbles in MCA**

### **Transcranial Doppler (TCD)**

- Non-invasive
- Can detect angiographic occlusions in MCA (>90%)
- Allows real-time readout of velocity changes in MCA

### ***When?***

- At baseline
- Throughout the procedure and for 1 additional hour

**Subjects who are positive for microbubbles in MCA will have brain MRI's done.**

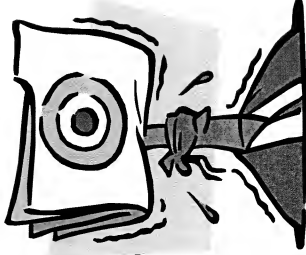


## Detect Effect of Foam Sclerosants on Brain

### Detection of micro-infarcts

#### Brain MRI's:

- T2 imaging
- Diffusion-Weighted Image MRI (DWI MRI),  
and
- Perfusion Weighted Image MRI (PWI MRI)





## Does deep vein thrombosis (DVT) occur with use of Foam Sclerosants?

YES.

Four patients with DVT in peroneal muscle – (bilateral in one patient)  
– reported by one physician using 2% aethoxysklerol foam

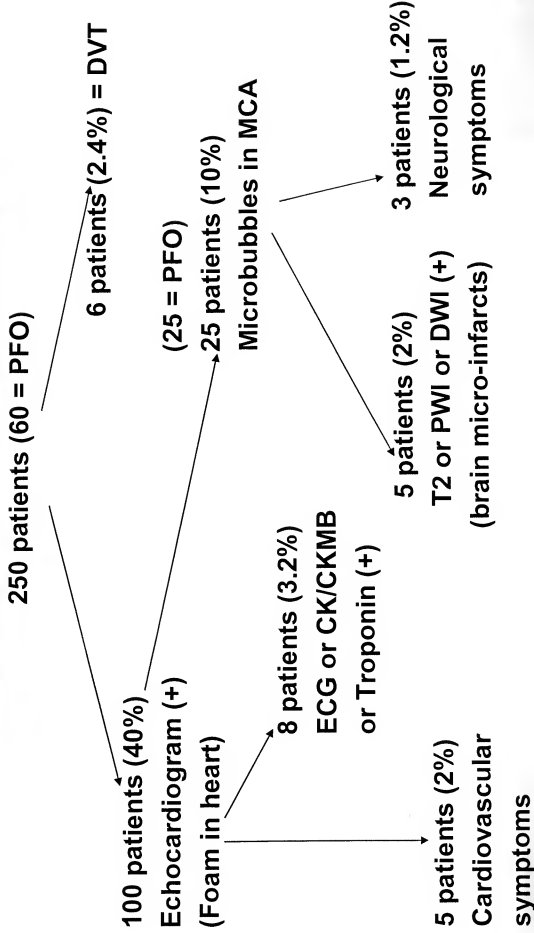
Two patients reported by one physician (used aethoxysklerol  
3% foam /1% liquid): one patient had antithrombin III defect and  
the other had heterozygous Factor V mutation.

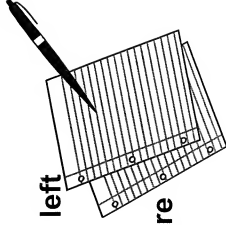
Literature: Three cases of thrombus propagation in deep vein  
system following foam injection.



# Safety Aspects of Foam Sclerosants

## Hypothetical Characterization





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## **Efficacy Issues related to Clinical Trials of Foam Sclerosants**

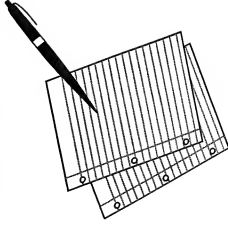
### **Standardize the treatment:**

**Dose:** concentration, amount and volume

**Administration:** Ultrasound-guided injection

***In vitro*** dose: bubble diameter, color of foam aspirate,  
presence of venospasm

**Document ALL in CRFs**



**MAINTAIN ALL RECORDS**



## **Efficacy Issues related to Clinical Trials of Foam Sclerosants**

**Specify the procedures:**

- Randomization
- Blinding
- Statistical Plan





## **Efficacy Issues related to Clinical Trials of Foam Sclerosants**

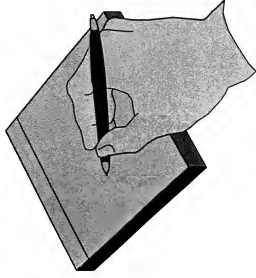
**Standardize the efficacy endpoint (surrogate):**

**What? E.g., complete occlusion of varicose veins or disappearance of a spider vein**

**How? E.g., duplex ultrasound and spectral display or digital images or photographs**

**When? E.g., 28 days post-treatment**

**What is (are) the “clinical” endpoint(s)?**





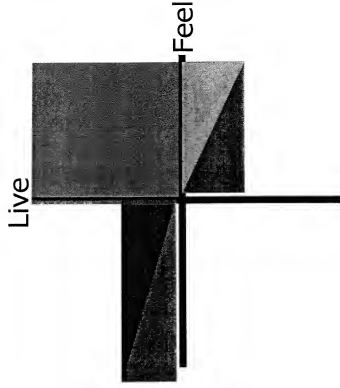
# Drugs should result in ...

⌘ Feeling better

- ☐ Functional status
- ☐ Hospitalization, other therapy
- ☐ Global assessment

⌘ Living longer

⌘ If you have to choose, then choice should make sense





**What is taking so long for the approval of  
aethoxysklerol (polidocanol)?**

**Efficacy!**

**Safety!**



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